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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/367,859	09/02/99	SAMSOONDAR J	5352-051

EXAMINER	
SODERQUIST,A	
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DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/367,859	Samsoondar
Examiner	**Art Unit**
Arlen Soderquist	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-18 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1 an interferant is a relative thing since it interferes with the analysis of another component of a sample. Since there is no analyte in claim 1 the process is either lacking steps related to the analysis of the analyte or the interferant is actually the analyte for claim 1 and the claims which are dependent therefrom. For examination purposes the interferant will be treated as the analyte since calling it an interferant does not change the fact that it is the only thing that a concentration is being determined.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claim 1 is rejected under 35 U.S.C. 102(b,e) as being anticipated by each of Chai, Fitch, Golden, Hamilton, Lin, Pascual-Marti, Phillips, Randall, Sagusa, Stimmel and Vink.

In the paper Chai teaches a fast determination of serum bilirubin with the interference from hemolysis and turbidity by three wavelength. In determination of bilirubin in serum by means of color reaction when hemolysis and turbidity are present, the reliability of the measurement is decreased by the interference from hemoglobin and other turbidities. Direct measurement of bilirubin in serum by three wavelength spectrophotometry at 500 nm, 450 nm and 370 nm instead of by color reaction, provides a fast, semi-micro and accurate way without the use of any reagents. Besides the rise of the baseline by blood cells and turbidities can be corrected without the consideration of hemolysis. Under the given experimental condition, the mean recovery is 96.3 +/- 2.41% (n = 6), coefficient of variation (CV) is 4.0%.

In the paper Fitch teaches measurement of urinary 3-methylhistidine with cationic-exchange resin. A simple method is presented for measurement of urinary

3-methylhistidine (3MH) using a cationic exchange resin treatment followed by colorimetric analysis. Equations are given to correct for the interference by histidine (4.3% by mole) in the colorimetric analysis. This correction is especially important for measurement of urinary 3MH in pregnant women or in other subjects with elevated histidine excretion. Good recovery of added standard and good reproducibility of results are documented. Preliminary data from a study of pregnant women are reported, suggesting an increased excretion of 3MH during pregnancy. Large day-to-day variability of 3MH excretion was observed within subjects. It is recommended that repeated measurements be done on each subject when determining 3MH excretion.

In the paper Golden presents a quantitative determination of bilirubin in urine. To 1 ml. of urine in a colorimeter tube, 8 ml. of 95% EtOH and 1 ml. of freshly prepared Ehrlich's diazo reagent are successively added. After 30 minutes, 0.25 ml. of concentrated HCl is added. The optical density of bilirubin is calculated from the equation: Y (at 575 mμ) = 1.05 × observed optical density (at 575 mμ) - 0.202 × observed optical density (at 450 mμ); Y × 6.2 = mg. % bilirubin. The equations are derived in detail. Application of the correction equation eliminates interference of nonbilirubin materials.

In the paper Hamilton describes a method for correcting of interference in spectrophotometric Evans blue dye determinations caused by hemolysis and (or) lipemia.

In the paper Lin teaches a correction method for determination of N-polyethoxylated alkyl amide in clay supernatant.

In the paper Pascual-Marti describes a The paper describes the theoretical and experimental study performed to extend the application of the Linear Absorbances Method to more complex systems, which present 2 spectral interferences. The curves of collinearity are developed and a theoretical study of them is carried out. The theoretical equations developed are experimentally tested on the determination of methyl orange in the presence of methyl red and cresol red and the influence of the variables involved in the Linear Absorbance Method is studied, too. The use of couples of collinear wavelengths of the interferants allows to obtain the concentration of a compound in the presence of 2 interfering substances.

In the patent Phillips teaches a method for determining the presence of an analyte in a fluid along with various components of an apparatus specifically designed to carry out the method. The method involves taking a reflectance reading from one surface of an inert porous matrix impregnated with a reagent that will interact with the analyte to produce a light-absorbing reaction product when the fluid being analyzed is applied to another surface and migrates through the matrix to the surface being read. Reflectance measurements are made at two separate wavelengths in order to eliminate interferences, and a timing circuit is triggered by an initial decrease in reflectance by the wetting of the surface whose reflectance is being measured by the fluid which passes through the inert matrix. The method and apparatus are particularly suitable for the measurement of glucose levels in blood without requiring separation of red blood cells from serum or plasma.

In the paper Randall discusses interference by hemolysis, icterus and lipemia in assays on the Beckman Synchron CX5 and methods for correction. As part of an evaluation of a Synchron CX5 analyzer (Beckman Instruments Inc. Brea, USA) a range of tests were examined for interference from hemolysis, bilirubin, and lipemia. Tests investigated were urea, creatinine, urate, total protein, albumin, Ca, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), γ-glutamyl transferase (GGT) and inorganic phosphate. Two types of interferences were found. One type is found on other analyzers and represents analytical difficulties with the measurement of that particular analyte. The other type of interference was a consequence of the bichromatic optical system used on the CX-5. This latter group includes Hb interference in the measurement of total protein and inorganic phosphate, and bilirubin interference with the measurement of total protein, glucose, and inorganic phosphate. Lipemia interfered with total protein, total bilirubin, inorganic phosphate, urate and glucose. Alternative and modified methods are proposed to improve the measurement of total protein, glucose, total bilirubin and inorganic phosphate. The use of the modified methods for glucose, inorganic phosphate, and total bilirubin are limited, at this time, by an error in the calculation algorithm used by the analyzer for two step or triggered chemistries, and to a lesser extent, by a reduction in sample throughput.

In the patent Sagusa teaches a colorimetric method for samples including interfering chromogens. Color former is added to blood serum sample color it, and measurements for specific components are determined based on the light absorbance caused by coloring. For one sample, a differential light absorbance between two wavelengths at each of long wavelength region, middle wavelength region and short wavelength region within a visible wavelength band is determined. The degree of chyle is determined from the measurements for the long wavelength region, the degree of hemolysis is determined from the measurements for the middle wavelength region, and the degree of icterus is determined from the measurements for the short wavelength region. The measurements for the specific components are then corrected by the degree of chyle, degree of hemolysis and degree of icterus to obtain highly correct measurements.

In the paper Stimmel teaches the use of a color correction equation with the Kober reagent for the estimation of the estrogens in human urine with low estrogen content. In satisfactory Kober tests (i.e., an L-520 mμ to L-420 mμ ratio greater than 3), for determination of estrone and estriol in urine, a brown color is produced with the Kober reagent by nonestrogenic chromogens when the urine has a low estrogenic titer. This causes overestimation, but can be corrected by using the equation Cx = L-520 mμ mixture - Bx (L-420 mμ mixture)/Kx(1 - AxBx) when Cx is the weight of the estrogen component of the test in γ, L is 2 - log of galvanometer reading, Ax is the ratio of L-420 mμ to L-520 mμ for Kober color test, Bx is the ratio of L-520 mμ to L-420 mμ for interfering chromogens, and Kx is the calibration constant for the Kober test on pure estrogen. The variations in spectrophotometric characteristics (at 420 and 520 mμ) of the brown color produced by the Kober reagent with chromatographic filtrate residues from estrogen-free urine were studied, and sufficient experimental data were obtained to evaluate the above constants. The overestimation in a 24-hour urine specimen is reduced to ± 7 γ of estrone, $\pm$ 10 γ of estradiol, and ± 5 γ of estriol. It is recommended that the color-correction equation be used whenever there is a L-520 mμ to L-420 mμ ratio less than 6.0. This method is sufficiently sensitive to indicate the mid-menstrual elevation of estrogen excretion in a normal female menstrual cycle.

In the paper Vink teaches direct spectrophotometry of bilirubin in serum of the newborn, with use of caffeine reagent. The caffeine reagent (Vink, K. L. J. et al., 1986) was used in setting up a bilirubin method for serum from neonates. This resulted in a 2-wavelength (465 and 528 nm) equation that fully corrects for HbO2 interferences. In combination with a bilirubin standard, this equation may be transformed into a simple relative formula for use with this simple dilution method. This 2-wavelength method was studied with neonate sera, comparing results with those by both the diazo method of B. T. Doumas et al. and the borate method of H. Hertz et al. (1974). This new method is independent of hemolysis and of the matrix of the sera.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 2-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sagusa as applied to claim 1 above, and further in view of Christenson, Leissing or Mullins and Simon. Sagusa does not teach interference by blood substitutes or detection of pseudohemolysis.

In the abstract Christenson discusses hemoglobin based blood substitutes and their interference with routine chemical tests.

In the abstract Leissing discusses modification of clinical chemistry methods to overcome interferences from diaspirin crosslinked hemoglobin (DCLHb.

In the paper Mullins discusses effects of Fluosol-DA (artificial blood) on clinical chemistry tests and instruments. Artificial blood must be added to the list of therapeutic agents that produce interference with diagnostic laboratory tests. Fluosol-DA (Alpha Therapeutic Corp., Los Angeles, CA), a stable 20% emulsion of perfluorocarbons in aqueous medium, is being evaluated in clinical trials as a blood substitute in the United States. They investigated its effects in blood and serum samples on test results and instruments in the clinical chemistry laboratory. The 20% emulsion was added to blood or serum specimens in amounts corresponding to the replacement of in-vivo plasma volumes of 10-50%, concentrations that would be expected in blood samples obtained from patients who have received Fluosol. Observed interferences mimicked those caused by high triglyceride concentrations in serum specimens: interference with chemical reactions and generation of spurious absorbance readings because of turbidity. These types of errors are often additive, and the cumulative effect may cause either erroneously high or low values for the analytes concerned. Because Fluosol may be used widely, although infrequently, for patients refusing blood transfusions on religious grounds and for patients with rare antibodies to red blood cells who require transfusion, laboratories analyzing specimens containing Fluosol should be aware of the potential errors.

In the paper Simon discusses a "pseudo-hemolytic" transfusion reaction caused by intravenous iron-dextran therapy. Intravenous iron-dextran therapy can cause a red-brown discoloration of the plasma, simulating a hemolytic transfusion reaction. A rapid and simple test to differentiate between true hemolysis and plasma discoloration due to circulating iron-dextran complexes is described.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include substances such as blood substitutes recognized by Christenson, Leissing or Mullins as interfering substances into the Sagusa correction method because of the recognized possibility for interference with clinical chemistry tests and the projected use of these substances in humans. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the Sagusa method to differentiate between true hemolysis and plasma discoloration due to circulating colored substances as taught by Simon because of the ability to

select wavelengths that will allow the effects of one chromogen to be removed from another chromogen as taught by Sagusa and the need to differentiate between true hemolysis and plasma discoloration due to circulating substances as taught by Simon.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additional art relates to correction of spectra.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner can normally be reached from about 5:30 AM to about 3:00 PM on Mondays and from about 7:30 AM to about 5:00 PM on Tuesday through Thursday and alternate Fridays.

For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Another number for official papers is (703) 305-3599. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Arlen Soderquist

June 28, 2001

ARLEN SODERQUIST
PRIMARY EXAMINER